

REMARKS

The amendments to the specification do not add new matter. Rather, they conform the specification to the recommendation of the Patent Office that the Applicants delete all remaining embedded hyperlinks.

The amendments to claims 31 and 32 merely conform the claims to the full text of the antecedent term. For these reasons, the amendments to the claims also do not add new matter.

BASES FOR OBJECTION/REJECTION

The Patent Office has objected to the specification based upon the Applicants' incorporation by reference.

The Patent Office has objected to the specification based upon the Applicants' use of embedded hyperlinks.

The Patent Office alleges that the Applicants claimed priority applications (USSN 60/153,093, filed Sep. 9, 1999 and 60/107,756, filed Nov. 10, 1998) fail to provide adequate support under § 112 for claims 27 and 31-37.

Claims 27 and 31-37 are rejected under 35 U.S.C. § 112, first paragraph for allegedly failing to comply with the written description requirement.

Claims 27 and 31-37 are rejected under 35 U.S.C. § 112, first paragraph for allegedly failing to comply with the enablement requirement.

Claims 27 and 31-37 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Patten (Current Opinion in Biotechnology, 8:724-733, December 1997) and Jamet (J. of Mol. Evolution, 33:226-236, 1991).

The Applicants will address each of these bases for rejection in Sections I-VI, respectively, which follow.

I. Incorporation by Reference

The Patent Office has objected to the specification based upon the Applicants' words of incorporation by reference. In this regard, the Patent Office **quotes** the Applicants' specification as reciting the following:

All publications are incorporated herein by reference, whether specifically noted or not.

[Official Action at page 2.]

However, the language that the Applicants actually employed in their specification at page 87, lines 11-13 actually recites something quite different:

All publications and patent applications herein are incorporated by reference to the same extent as if each

individual publication or patent application was **specifically** and individually indicated to be incorporated by reference.

[Emphasis added in bold.]

The words in common between the Patent Office's contention and the actual text from the specification are bolded above. The Patent Office contends that such "omnibus language fails to specify what specific information applicant seeks to incorporate from each and every document cited and similarly fails to teach with detailed particularity just where that specific information is to be found in each of said cited documents." [Official Action at page 2.] The Applicants respectfully disagree.

The Applicants have not cited the references "in their entirety" as is done in many patent applications. Rather, a reference is cited for supporting the particular principle stated in the preceding sentence. For example, on page 58 of the specification, the Applicants disclose that Cauliflower mosaic virus may be used to introduce foreign DNA into plant cells and then cite to the relevant eleven (11) pages in a book (**not the whole book**) by Hohn et al., to incorporate the relevant pages and to show that this was already well-known in the art as far back as 1982:

Cauliflower mosaic virus (CaMV) may also be used as a vector for introducing the foreign nucleic acid into plant cells (**Hohn et al., (1982) "Molecular Biology of Plant Tumors," Academic Press, New York, pp.549-560**; Howell, U.S. Pat. No. 4,407,956). CaMV viral DNA genome is inserted into a parent bacterial plasmid creating a recombinant DNA molecule which can be propagated in bacteria. After cloning, the recombinant plasmid again may be cloned and further modified by introduction of the desired DNA sequence into the unique restriction site of the linker. The modified viral portion of the recombinant plasmid is then excised from the parent bacterial plasmid, and used to inoculate the plant cells or plants.

[Specification at page 58, lines 9-17; emphasis added in bold.]

Thus, when the Applicants' specification cites to a book that has a disclosure that is broader and more comprehensive than the information being referenced in the preceding sentence, the Applicants' specification cites to the relevant pages.

Likewise, when the Applicants' specification cites to a publication, it is because the publication supports the principle or fact in the sentence (if it appears as a parenthetical in the sentence) or in the preceding sentence (if the publication appears after the sentence). For example, at page 58, the specification cites to a three (3) page publication in Nature that discloses a method for introducing nucleic acids into a cell using the gene gun ("**high velocity ballistic penetration by small particles**"):

Another **method** of introduction of nucleic acid segments is **high velocity ballistic penetration by small particles** with the nucleic acid either within the matrix of small beads or particles, or on the surface (Klein et al., (1987) Nature 327:70-73). Although typically only a single introduction of a new nucleic acid segment is required, this method particularly provides for multiple introductions.

[Specification at page 58, lines 18-22; emphasis added in bold.]

It is respectfully submitted that if the publishers of Nature thought that the disclosed method could have been described with greater brevity, they would have required the authors to have shortened their publication. Likewise, when the Applicants otherwise incorporate a cited method by reference into their specification, the method and variations of it are described in the publication as a whole. The citation to a method should not be confused with citing to a fact (such as molecular weight, number of subunits or wavelength), which can be found on a single page of a publication. Thus, it is submitted that the Applicants' incorporations by reference are proper and sufficiently specific. If the Patent Office perceives otherwise, then it should indicate the specific citations which it believes are too broad so that they can be addressed.

The Applicants' incorporations by reference are appropriate for another reason. The MPEP also provides that a specification should not be repetitive. In the present case, the Applicants' specification averages about 3 citations per page and the specification contains 87 pages. A sentence incorporating by reference each publication in its entirety would require 1 ½ lines. Multiplying the 87 pages times 1 ½ lines per page would yield 130.5 lines of redundant incorporations. Since the Applicants' specification averages 31 lines per page, there would be an additional 4.2 pages of text devoted exclusively to reciting an incorporation

by reference. Applicants tried to avoid this redundancy by using a blanket incorporation of the cited references for the methods, principles and facts cited. The basis for each citation is clear from the context in which each citation was presented. The Patent Office's argument would have validity if all of the citations appeared at the end of the document and did not have any context to any sentence. However, this is not the case. The Applicants method of citation is the very method used by those skilled in the art in their own publications. Hence, those skilled in the art understand the context and of the Applicants' citation. Moreover, consistent with Patent law, the Applicants have incorporated those cited references into the specification in the least redundant manner possible, so that the Applicant's already long specification would not be cumbersome to read.

For all these reasons, the Applicants incorporation by reference is proper and would be understood by those skilled in the art as being as possible based upon what is being incorporated. The withdrawal of this basis for objection is respectfully requested.

II. Embedded HyperLinks

The Patent Office has objected to the specification based upon the Applicants' use of embedded hyperlinks. The applicants have searched out each use of "http" and the hyperlink associated with it and amended the specification to delete the "embedded hyperlink." However, out of an abundance of caution, the applicants have in certain instances retained disclosure of the appropriate web-sites that one skilled in the art could go to so as to obtain further information or to contact a manufacturer. In these latter instances, the citations do not include an "embedded hyperlink" that would otherwise allow one who is viewing a patent or published application on the internet to be able click on the hyperlink and be transported to the appropriate website. For all these reasons, the amendments to the specification have rendered moot this basis for objection to the specification.

III. Priority Claim

The Patent Office alleges that the Applicants claimed priority applications, USSN 60/153,093, filed Sep. 9, 1999 and 60/107,756, filed Nov. 10, 1998, fail to provide adequate support under § 112 for claims 27 and 31-37. The Applicants respectfully disagree.

A copy of claim 27 appears below:

27. (previously presented) A method for obtaining an isolated polynucleotide comprising a sequence encoding a protein having Rubisco carboxylation activity, the method comprising:

recombining a plurality of parental polynucleotide species encoding at least one protein having Rubisco carboxylation activity under conditions suitable for sequence shuffling to form a resultant library of sequence-shuffled polynucleotides;

transferring said library into a plurality of host cells, thereby forming a library of transformants wherein sequence-shuffled Rubisco polynucleotides are expressed;

identifying at least one **transformant** from said library that expresses an enhanced protein having a Rubisco carboxylation activity that is **enhanced** to an extent that is statistically significant relative to the Rubisco carboxylation activity of proteins encoded by the plurality of parental polynucleotide species, wherein the identified transformant contains a polynucleotide comprising a sequence encoding the enhanced protein; thereby obtaining a polynucleotide comprising a sequence encoding the enhanced protein.

[Specification at claim 27; emphasis added in bold.]

Support for claim 27 is found in claim 1 of Applicants' provisional application USSN 60/107,756, filed Nov. 10, 1998:

1. **A method for obtaining an isolated polynucleotide encoding an enhanced Rubisco protein having Rubisco catalytic activity** wherein the K_m for CO_2 is significantly lower than a protein encoded by a parental polynucleotide encoding a naturally-occurring Rubisco enzyme, **the method comprising:**

recombining sequences of a plurality of parental polynucleotide species encoding at least one Rubisco sequence [protein] under conditions suitable for sequence shuffling to form a resultant library of sequence-shuffled Rubisco polynucleotides;

transferring said library into a plurality of host cells forming a library of transformants wherein sequence-shuffled Rubisco polynucleotides are expressed;

selecting for enhanced growth at low CO_2/O_2 ratios or assaying individual or pooled transformants for Rubisco catalytic activity to determine the relative or absolute K_m for CO_2 and thereby identifying at least one enhanced transformant that

expresses a Rubisco activity which has significantly lower K_m for CO_2 than the Rubisco activity encoded by the parental sequence(s);

recovering the sequence-shuffled Rubisco polynucleotide from at least one enhanced transformant.

[Specification at claim 1; emphasis added in bold.]

The bolded language in claim 1 of USSN 60/107,756 is the same or substantially the same language as later recited in claim 27 of the present pending application. Thus claim 1 of USSN 60/107,756 provides written description support for claim 27 of the present invention.

Additional support for claim 27 of the present application is found in the specification of USSN 60/107,756 at page 8, lines 10-22 as shown below:

The invention provides a method for obtaining an isolated polynucleotide encoding an enhanced Rubisco protein having Rubisco catalytic activity wherein the K_m for CO_2 is significantly lower than a protein encoded by a parental polynucleotide encoding a naturally-occurring Rubisco enzyme, the method comprising: (1) **recombining** sequence of a plurality of parental polynucleotide species encoding at least one Rubisco sequence under conditions suitable for sequence shuffling to form a resultant library of sequence-shuffled Rubisco polynucleotides, (2) **transferring** said library into a plurality of host cells forming a library of transformants wherein sequence-shuffled Rubisco polynucleotides are expressed, (3) assaying individual or pooled transformants for Rubisco catalytic activity to determine the relative or absolute K_m for CO_2 and **identifying** at least one **enhanced transformant** that expresses a Rubisco activity which has significantly lower K_m for CO_2 than the Rubisco activity encoded by the parental sequence(s), (4) recovering the sequence-shuffled Rubisco polynucleotide from at least one enhanced transformant.

[Emphasis added in bold.]

Thus, the method of claim 27 has written support going back to the claimed priority application USSN 60/107,756, filed Nov. 10, 1998.

Separately, claims 31-37 of Applicants' invention have written support going back to the claimed priority application USSN 60/107,756, filed Nov. 10, 1998. Specifically, claim 31, which is directed to the method of claim 27, "wherein the **enhanced protein** has a

K_m for CO₂ that is less than that of proteins encoded by the plurality of [parental] polynucleotide species, to an extent that is statistically significant,” has written support in the priority application (USSN 60/107,756) at page 8, lines 18-21 (“(3) assaying individual or pooled transformants for Rubisco catalytic activity to determine the relative or absolute K_m for CO₂ and **identifying at least one enhanced transformant that expresses a Rubisco activity which has significantly lower K_m for CO₂ than the Rubisco activity encoded by the parental sequence(s)**”); emphasis added in bold.

Claim 32, which is directed to the method of claim 27, “wherein the enhanced protein has a **K_m for O₂ that is greater than that of proteins encoded by the plurality of [parental] polynucleotide species, to an extent that is statistically significant,”** has written support in the priority application (USSN 60/107,756) at page 8, line 26 to page 9, line 1 (“If it is desired to obtain a sequence-shuffled Rubisco encoding a Rubisco enzyme having an increased K_m for O₂, step 3 comprises assaying individual or pooled transformants for Rubisco catalytic activity to determine the relative or absolute K_m for O₂ and identifying at least one enhanced transformant that expresses a Rubisco activity which **has significantly higher K_m for O₂ than the Rubisco activity encoded by the parental sequence(s)**.”); emphasis added in bold.

Claim 33, which is directed to the method of claim 27, “wherein the plurality of **parental polynucleotide species encodes at least one Rubisco Form I L subunit,**” has written support in the priority application (USSN 60/107,756) at page 5, lines 30 to page 6, line 6 (“In an aspect, the invention provides a **polynucleotide sequence encoding an [sic] shuffled L subunit of a Form I hexadecimetric Rubisco,** wherein the shuffled L subunit possesses a detectable enzymatic activity wherein: (1) K_m for CO₂ is significantly lower than a L subunit protein encoded by a parental polynucleotide encoding a naturally occurring Rubisco enzyme, (2) the K_m for O₂ is significantly higher than an **L subunit protein encoded by a parental polynucleotide . . .**”) and at page 6, lines 22-23 (“In an aspect, the invention provides an improved L subunit of a Form I Rubisco, or shufflant thereof, and a polynucleotide encoding same.”); emphasis added in bold.

Claim 34, which is directed to the method of claim 27, “wherein the plurality of parental polynucleotide species encodes at least one Rubisco Form I S subunit,” has written support in the priority application (USSN 60/107,756) at page 6, lines 11 to 19 (“In

an aspect, the invention provides a **polynucleotide sequence encoding an [sic] shuffled S subunit of a Form I hexadecimetric Rubisco**, wherein the shuffled S subunit possesses the property of complexing with an unshuffled, complementing L subunit thereby resulting in a multimer (e.g., hexadecimetric L_8S_8) having a detectable enzymatic activity wherein: (1) K_m for CO_2 is significantly lower than that of a Rubisco protein containing the S subunit encoded by a parental polynucleotide encoding a naturally occurring S-subunit of Rubisco, (2) the K_m for O_2 is significantly higher than that of a Rubisco protein containing an **S subunit protein encoded by a parental polynucleotide encoding a naturally occurring subunit of Rubisco . . .**”); emphasis added in bold.

Claim 35, which is directed to the method of claim 27, wherein “the plurality of parental polynucleotide species encodes at least one Rubisco Form II subunit,” has written support in the priority application (USSN 60/107,756) at page 7, lines 11-12 (“In an aspect, the invention provides an improved L subunit of a Form II Rubisco, or shufflant thereof, and a polynucleotide encoding same.”); emphasis added in bold.

Claim 36, which is directed to the method of claim 27 “further comprising a **selectable marker gene** which affords a **means of selection** when expressed in **chloroplasts**,” has written support in the priority application (USSN 60/107,756) at page 6, line 28 to page 7, line 3 (“It can be desirable for such a polynucleotide transgene to be transmissible via germline transmission in a plant; in the case of *rbcL* sequences transferred to chloroplasts, it is often accompanied by a **selectable marker gene** which affords a **means to select** for progeny which retain **chloroplasts** having the *rbc* shuffled sequence.”; and at page 7, line 12, (“In some embodiments, the polynucleotide will be operably linked to a transcription regulation sequence forming an expression construct, which may be linked to a **selectable marker gene**”); emphasis added in bold.

Claim 37, which is directed to the method of claim 36, wherein “the sequence encoding the enhanced protein and the selectable marker gene are **flanked by an upstream flanking recombinogenic sequence having sufficient sequence identify to a chloroplast genome sequence to mediate efficient recombination** and a **downstream flanking recombinogenic sequence having sufficient sequence identify to a chloroplast genome sequence to mediate efficient recombination**,” has identical written support in the priority application (USSN 60/107,756) at originally filed claim 15 (“A polynucleotide comprising:

(1) a sequence encoding a shuffled Rubisco Form I L subunit gene (rbcL) linked to (2) a selectable marker gene which affords a means of selection when expressed in chloroplasts, and, optionally, **flanked by (3) an upstream flanking recombinogenic sequence having sufficient sequence identity to a chloroplast genome sequence to mediate efficient recombination** and (4) **a downstream flanking recombinogenic sequence having sufficient sequence identity to a chloroplast genome sequence to mediate efficient recombination,**”) and at page 22, lines 4-11 (“With reference to expression cassettes which are designed to function in chloroplasts, such as an expression cassette encoding a large subunit of Rubisco (rbcL) in a higher plant, the expression cassette comprises the sequences necessary to ensure expression in chloroplasts – typically the Rubisco L subunit encoding sequence is **flanked** by two **regions of homology to the plastid genome so as to effect a homologous recombination with the chloroplastid genome**; often a selectable gene is also present within the flanking plastid DNA to facilitate selection of genetically stable transformed chloroplasts in the resultant transplastonic plant cells (citations omitted).”).

For all these reason, pending claims 27 and 31-37 are entitled to their claimed priority filing date of 11/10/98 because they have written description support in claimed priority application USSN 60/107,756, filed 11/19/98.

IV. 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 27 and 31-37 are rejected under 35 U.S.C. § 112, first paragraph for allegedly failing to comply with the written description requirement. The Patent Office has asserted various bases for rejection which the Applicants will address in turn. According to the Patent Office, “claim 27 has been interpreted as encompassing the modification of an infinite number [of] ‘parental polynucleotide species’ that encode any polypeptide that has any level of RUBISCO (ribulose-1,5-bis-phosphate carboxylase) carboxylation activity.” [Official Action at page 5.] The Applicants wish to point out that they are claiming a method – not a composition of matter. If the Applicants were claiming a method of shoveling dirt, they would not have to provide a composition of every possible soil type that could be dug by the method to satisfy the written description requirement. Rather, it is sufficient that the Applicants provide a written description of the steps utilized, whether the claimed steps are novel steps or a novel combination of steps wherein the individual steps (but not the

combination) are known in the art. The fact that the Applicants' method is applicable to any RUBISCO enzyme is not a basis for rejection. By further analogy, the fact that a method of waxing an auto can be applied to an infinite number of autos, including those yet to be conceptualized and built, does not inherently render the method as lacking written description.

In relation to this first basis for rejection, the Patent Office has failed to meet its burden by providing evidence why one skilled in the art would not consider the Applicants' disclosed method applicable to any RUBISCO enzyme. *See In re Alton*, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996) ("If on the other hand, the specification contains a description of the claimed invention, albeit not *in ipsius verbis* (in the identical words), then the examiner or Board, in order to meet the burden of proof, must provide reasons why one of ordinary skill in the art would not consider the description sufficient.") In contrast, the Patent Office has cited and relied upon the reference –Patten—for disclosing the art recognized "**broad applicability**" of DNA shuffling to **any protein** (or **any enzyme**) of **any kind**:

While **Patten et al., teach of applying DNA shuffling to genes**, including genes that exist in subunits, Patten et al., do not explicitly teach of performing DNA shuffling on the parental polynucleotides of RUBISCO (ribulose1,5-bisphosphate carboxylase). . . .

In view of the **explicit guidance**, and **broad applicability** of DNA shuffling to proteins in general, the **ordinary artisan** would have had a most reasonable expectation of success.

[Official Action at pages 10-11; emphasis added in bold.]

By use of the phrases "**ordinary artisan**," "**broad applicability**" and "**explicit guidance**" the Patent Office has acknowledged that one skilled in the art (*i.e.*, "the ordinary artisan") would have no reason to doubt that the **four pages** of non-table text in Patten is sufficient written description ("**explicit guidance**") for the ordinary artisan to apply DNA shuffling to **any enzyme**. Thus, the acknowledgement by the Patent Office that the **four pages** of "**explicit guidance**" in Patten that would provide an ordinary artisan with knowledge sufficient to shuffle **any enzyme** is convincing evidence that the **eighty six (86) pages** of written description in the Applicants' specification would reasonably convey to the ordinary artisan that the Applicants' had possession of the claimed method of shuffling a **single enzyme family** - RUBISCO. Further, one of the co-authors of Patten, Willem Stemmer, is also a co-inventor

of the present invention. Therefore, it is inconceivable that Stemmer, as a co-author of the allegedly sufficient reference Patten, did not convey in the 86 pages of his specification that he (and his co-inventors) had possession of the claimed method of improving the **single** enzyme - RUBISCO.

As its second basis for rejection, the Patent Office contends that “[s]aid claim 27, and claims 31-37, which depend therefrom, have also been interpreted as encompassing the production and screening of an **infinite number** of transformants.” [Official Action at page 5; emphasis added in bold.] The Patent Office then goes on to state that “[t]he originally filed application does not support the position that applicant was in possession of a method whereby **any number** of transformants could be screened.” [Official Action at page 5; emphasis added in bold.] As support for its position, the Patent Office relies upon the declared statement by Genhai Zhu that “It would be physically impossible to screen more than a tiny fraction of $[1 \times 10^{16}]$ cells.” [Official Action at pages 5-6 (bridging sentence), citing to ¶8 of the Zhu declaration.] However, the Patent Office’s reliance upon Zhu’s statement is misplaced because ¶8 of the Zhu declaration is directed to the method disclosed in Spreitzer. Specifically, the method of Spreitzer being discussed in paragraph 8 is directed to making two point mutations (instead of one) in RUBISCO and screening each for enhanced activity. The relevant paragraph in Spreitzer states the following:

It is clear that it would take more than a single amino acid substitution to make a better Rubisco. However, we should not give up hope merely because the direct-selection experiments have been unsuccessful. The probability for selecting a single, specific mutation within the *C. reinhardtii* *rbcL* gene is about 1×10^{-8} cells. If **two specific amino acid substitutions** are required simultaneously to make a better Rubisco, **more than 1×10^{16} cells** would need to be subjected to **selection**. **There are fewer cells than this living in all the *Chlamydonas* laboratories on the planet.**

[Spreitzer at page 416; emphasis added in bold.]

The corresponding statement in ¶8 of the Zhu Declaration, which comments on Spreitzer states the following:

8. This state of affairs is reflected in the Spreitzer reference. . . . In a similar experiment , Spreitzer et al screened greater than 1×10^9 mutagenized *C. reinhardtii* cell without finding a single Rubisco with improved catalytic constants. . . . Spreitzer concludes by stating that it will take more than a single amino acid substitution to make a better Rubisco, but if **two amino acid substitutions** are required simultaneously to make a better Rubisco, **more than 1×10^{16} cells** would need to be subjected to **selection**. It would be **physically impossible** to screen more than a tiny fraction of this number of cells.

[Zhu Declaration at ¶8; emphasis added in bold.]

Thus, it is clear that Zhu's comments were directed to Spreitzer's method of introducing all possible point mutations into a RUBISCO protein and then screening all possible mutants which would number 10^{16} mutants and would require 10^{16} cells to screen them individually for activity.

However, Patten, which is cited by the Patent Office as a reference for obviousness, distinguishes between DNA shuffling, such as employed by the Applicants, and point mutagenesis, such as employed by Spreitzer:

Iterative cassette or **point mutations** can overcome some of these limitations; however, as discussed below, **DNA shuffling profoundly accelerates the process**.

[Patten at page 724, col. 2; emphasis added in bold.]

* * *

Recent progress with **DNA shuffling** has clearly demonstrated the utility of recombination for **accelerating molecular evolution** through simultaneously permitting both **single mutations** and **large sequence blocks** (Table 1). DNA shuffling combined with focused selection pressure in the laboratory will allow one to **rapidly evolve genes** for a wide variety of industrial applications

[Patten at page 725, col. 1; emphasis added in bold.]

* * *

Thus, **in contrast to classical breeding techniques, DNA shuffling** allows one to readily combine DNA derived from separate species

or genera. This **results in a much more sparse sampling of sequence space** (Figure 3b), in which the **average similarity between library members is much lower than with other strategies**. Sparse sampling yields mutants that, after a single cycle, are **far more divergent** from the parental genes **than** is possible with single gene shuffling or **point mutation strategies**. This recent experiment demonstrates that cross-species recombination is a **remarkable accelerant** of molecular evolution.

[Patten at page 725, col. 2; emphasis added in bold.]

Thus, Patten distinguishes DNA shuffling such as employed by the Applicants from the point mutation technique of Spreitzer, stating that DNA shuffling “**profoundly accelerates the process**” and yields mutants that are “**far more divergent**” than “**point mutation strategies**.” Accordingly, one skilled in the art would have no reason to believe that the Applicants’ claimed method would result in an “infinite number of transformants” to be screened. Moreover, if the Patent Office truly believed that Spreitzer’s disclosed method with its 10¹⁶ transformants was the same as Applicants’ claimed method, then Spreitzer would be cited as anticipatory prior art – and it is not. For these reasons, this basis for rejection of claims 27 and 31-37 under 35 U.S.C. § 112, first paragraph, for failure to satisfy the written description requirement has been rebutted.

As its third basis for rejection, the Patent Office contends that the specification does not provide a written description of what “polynucleotide sequences are essential to exhibiting any level of RUBISCO carboxylation activity.” [Official Action at page 6.] The Patent Office does acknowledge that “the specification does provide various ‘citations’ disclosing polynucleotide sequences. [Official Action at page 6.] However, the Patent Office goes on to contend that “such citations have been improperly incorporated by reference and cannot therefore, be relied upon for satisfaction of the written description requirement.” [Official Action at page 6.] The Applicants respectfully disagree.

The basis underlying the Patent Office’s contention that Applicants’ incorporation by reference is improper is that the Applicants statement of incorporation “fails to specify what specific information applicant seeks to incorporate by reference from each and every document cited and similarly fails to teach with particularity just where that specific information is to be found in each of said cited documents.” [Official Action at page 2.] The Applicants have addressed the issue of incorporation by reference in Section I herein.

However, the Applicants will again address the issue of incorporation in relation to the polynucleotide sequences encoding RUBISCO. Specifically, the specification discloses the following sources for RUBISCO genes, which published sources of the genes are incorporated by reference:

[0089] **All sequences referred to herein** or equivalents which function in the disclosed methods can be retrieved by GenBank database file designation or a commonly used reference name **which is indexed in GenBank or otherwise published are incorporated herein by reference** and are publicly available. Over 1,000 **Rubisco** homologues are available, e.g., in GenBank.

[Specification at page 33, lines 14-18; emphasis added in bold.]

Thus, in relation to the publications disclosing the gene sequences encoding RUBISCO, the Applicants' above statement of incorporation discloses that the **specific** information – **gene sequences for RUBISCO** – that are to be incorporated by reference from the cited references. Accordingly, the Patent Office was incorrect in making the blanket assertion that the statement of incorporation “fails to specify **what specific information** applicant seeks to incorporate by reference from each and every document cited.” [See the Official Action at page 2; emphasis added in bold.] The Applicants have utilized multiple statements of incorporation; and the Applicants' statement of incorporation regarding the polynucleotide sequences is proper and sufficiently **specific** as to the fact that the sequence is being incorporated. When the Applicants' statements of incorporation are included in the disclosure as they should be, the Applicants' disclosure satisfies the written description requirement under 35 U.S.C. § 112, first paragraph.

By way of example, the following are disclosures of incorporated sources of RUBISCO genes (parental polynucleotides) that are incorporated into the Applicants' specification.

[0096] A variety of **Rubisco gene and gene homologue sources** are known and can be used in the recombination processes herein. For example, as noted, a variety of references herein describe such genes. For example, **Croy, (ed.) (1993) Plant Molecular Biology Bios Scientific Publishers, Oxford, U.K. describe several Rubisco genes and sequence sources in public databases.** Examples of public databases that include Rubisco sources

include: **Genbank**; **EMBL**; as well as, e.g., the protein databank, Brookhaven Laboratories; the University of Wisconsin Biothechology Center, the DNA databank of Japan, Laboratory of genetic Information Research, Misuina, Shizuda, Japan. As noted, over **1,000 different Rubisco homologues are available in Genbank alone.**

[Specification at page 37, lines 9-18; emphasis added in bold.]

* * *

[0130] In an embodiment, the method employs at least one parental **polynucleotide sequence that encodes a Rubisco subunit of a marine algae**, such as for example and not limitation *Cylindrotheca fusiformis*, *Olisthodiscus luteus*, *Cryptomonas*, and *Porphyridium*, among others having Rubisco enzymes with a high ratio of carboxylase to oxygenase activity (**Read B A and Tabita F R (1994) Arch. Biochem. Biophys. 312:210.**

[Specification at page 47, lines 12-17; emphasis added in bold.]

* * *

[0145] Example photosynthetic bacteria for obtaining the **rbcL gene(s)** include *Rhodobacter shaeroides* (**Falcone et al. (1988) J. Bact. 170: 5**), *Rhodospirillum rubrum* (**Falcone et al. (1991) J. Bact. 173: 2099**; **Falcone D L and Tabita R (1993) J. Bact. 175: 5066**; **Narange et al. (1984) Mol. Gen. Genet. 193: 220**)) and the like.

[Specification at page 53, lines 8-11; emphasis added in bold.]

* * *

[146] Example photosynthetic dinoflagellate sources for **rbcL genes** include those from *Gonyaulax polyedra* (**Morse et al. (1995) Science 263: 1522**), *Amphidinium carterae* (**Whitney et al. (1998) Aust. J. Plant Physiol. 25: 131**), and *Symbiodinium* (**Rowan et al. (1996) Plant Cell 8: 539**).

[Specification at page 53, lines 24-27; emphasis added in bold.]

* * *

[0242] Rubisco genes of prokaryotes are composed of only the large subunit and are called Form II enzymes. These are present in organisms like Rhodobacter, Thiobacillus, dinoflagellates etc. (Watson GMF and Tabita F (1997) FEMS Microbiology Letters 146: 13-22). **A number of Form II Rubisco have been cloned and sequenced and are accessed from gene bank (Robinson et. al J. Bacteriol. 180: 1596-99).** Primers are designed for these genes based on consensus sequences and genes from various organisms are isolated as described in literature (Robinson et al). Alternately, all of the genes are synthesized.

[Specification at page 80, lines 6-13; emphasis added in bold.]

* * *

[0243] The Form II **genes** from various prokaryotes and dinoflagellates (**Morse et al. (1995) Science 268: 1622-1624, Rowan et al. (1996) The Plant Cell 8: 539-553**) display high degree of homology are shuffled according to the method of the invention. Briefly,

[Specification at page 80, lines 14-17; emphasis added in bold.]

* * *

[0245] Cyanobacterial Rubisco resemble those of higher plant forms in that they are composed of small and large subunits assembled into a hexadecimeric holoenzyme. The two subunits are **coded by rbcS and rbcL genes. These genes have been functionally expressed in E. coli (Tabita F R and Small C L 1985. PNAS 82: 6100-6103, van der Vies S M et al. The EMBO Journal 5: 2439-2444).** Both these genes are isolated and cloned in E. coli by described methods.

[Specification at page 81, lines 10-15; emphasis added in bold.]

For all these reasons, the rejection of claims 27 and 31-37 under 35 U.S.C. § 112, first paragraph, for allegedly failing to satisfy the written description requirement has been rebutted. The withdrawal of this basis for rejection is respectfully requested.

V. 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 27 and 31-37 are rejected under 35 U.S.C. § 112, first paragraph for allegedly failing to comply with the enablement requirement. According to the Patent Office,

the “specification was not described in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.” [Official Action at page 6.] As support for its position, the Patent Office ties its rejection for lack of enablement, to its prior rejection for alleged failure to satisfy the written description requirement, stating “It is well settled that one cannot enable an invention that they do not possess.” [Official Action at page 7.] However, the rejection for alleged failure to satisfy the written description requirement is now rebutted. *See* Section IV *supra*. Because the rejection for alleged failure to satisfy the written description requirement has been rebutted, the tied rejection for alleged lack of enablement is also been rebutted.

Separately, the Patent Office states that the legal basis underlying its rejection for alleged lack of enablement is that “It is well settled that one cannot enable an invention that they do not possess.” [Official Action at page 7.] However, this basis for rejection is legally erroneous because it is contrary to Federal Circuit law. The enablement and written description requirements are separate and distinct from one another. *See Vas-Cath v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991) (“This court in *Wilder* (and the CCPA before it) clearly recognized, and we hereby affirm, that 35 U.S.C. § 112, first paragraph, requires a ‘written description of the invention’ which is separate and distinct from the enablement requirement.”). Contrary to the Patent Office’s stated position, one may satisfy the enablement requirement without satisfying the written description requirement:

Some commentators **have had difficulty in understanding how one may have enabled an invention, but not described it.** They believe they must coincide. As an example of how the written description and enablement provisions differ in chemistry, however, **one may have readily enabled the making of an invention, but still not have described it.** For example, a propyl or butyl compound may be made by a process analogous to a disclosed methyl compound, but, in the absence of a statement that the propyl and butyl compounds are part of the invention, they have not been described and they are not entitled to a patent.

[*Enzo Biochem v. GenProbe*, 63 USPQ2d 1618, 1623-4 (Fed. Cir. 2002; emphasis added in bold.)]

This holding was more recently stated in *University of Rochester v G.D. Searle*, 69 USPQ2d 1886, 1891 (Fed. Cir. 2004) (“it is possible for a specification to *enable* the practice of an

invention as broadly as it is claimed, and still not describe that invention”). Similarly, one may satisfy the written description requirement without enabling the invention. *University of Rochester*, 69 USPQ2d at 1891 (“Thus, an invention may be described without an enabling disclosure of how to make it.”); *see also Vas-Cath*, 19 USPQ2d at 1117 (“drawings alone may be sufficient to provide the ‘written description of the invention’ required by § 112, first paragraph.”). The written description requirement looks to what is disclosed in the four corners of the specification. In contrast, the enablement requirement can look beyond the disclosures in the specification to the information known in the art:

the applicant “may begin at the point where his invention begins, and describe what he has made that is new and what it replaces of the old. **That which is common and well known is as if it were written out in the patent and delineated in the drawings.**”

[*In re Howarth*, 210 USPQ 689, 692 (CCPA 1981), citing *Webster Loom Co. v. Higgins*, 105 US 580, 586 ; emphasis added in bold.]

Consistent with this CCPA holding based upon Supreme Court precedent, the Federal Circuit set forth the test for enablement which not only looks to the **disclosures in the specification** but also the **information known in the art**:

The test of enablement is whether one reasonably skilled in the art could make or use the invention **from the disclosures in the patent coupled with the information known in the art** without undue experimentation.

[*U.S. v. Teletronics*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046, 109 S.Ct. 1954 (1989); emphasis added in bold.]

Thus, to satisfy the enablement requirement, the Applicant may rely upon the disclosures in the specification and the knowledge in the art. Regarding the “knowledge in the art,” the Federal Circuit has held that “**a patent need not teach and preferably omits, what is well known in the art.**” *Hybritech v. Monoclonal Antibodies Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1987). Thus, in the present case, the Applicant is able to “begin at the point where his invention begins” and use the art as cited by the Applicants in their specification, as evidence of the information that is known in the art, even if the art is not incorporated by reference. For these reasons, the

rejection of claims 27 and 31-37 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement is rebutted.

Separately, the Applicants' specification is enabling for another reason. In its rejection for obviousness, the Patent Office has cited to Patten for allegedly disclosing that DNA shuffling has general applicability to all proteins. Patten has about four pages of actual text. The remaining 4 ½ pages of Patten are tables and figures. As a matter of law, any disclosure cited for obviousness must be enabling. *See Motorola Inc. v. Interdigital Technology Corp.*, 43 USPQ2d 1481, 1489 (Fed. Cir. 1997) ("In order to render a claimed apparatus or **method** obvious, the prior art **must enable** one skilled in the art to make and use the apparatus or **method**."). Thus, implicit in the Patent Office's citation to Patten is the Patent Office's acknowledgement that Patten is an enabling reference, *i.e.*, a reference that would enable the shuffling of any polynucleotide encoding any protein. In relation to Patten, the Patent Office has stated

In view of the **explicit guidance**, and **broad applicability** of DNA shuffling to **proteins in general**, the ordinary artisan would have had a most reasonable expectation of success.

[Official Action at pages 10-11; emphasis added in bold.]

If the four page disclosure of Patten is sufficiently "**explicit**" to enable one skilled in the art to DNA shuffle "proteins in general" (*i.e.*, **any protein of any kind**), then the Applicants' 86 page specification that is devoted to a **single** protein should be even "**more explicit**" and at least as "**enabling**" if not more "more enabling." This argument becomes even more compelling when one considers that Stemmer, a co-author of Patten, is also a co-inventor of the present invention. If Stemmer could enable all proteins in 4 pages, he certainly would have enabled a single protein in 86 pages. For these reasons also, claims 27 and 31-37 are enabled by the disclosure in the Applicants' specification coupled with the information known in the art. *See U.S. v. Telectronics*, 8 USPQ2d at 1223. The withdrawal of this basis for rejection is respectfully requested.

VI. 35 U.S.C. § 103(a) Patten in view of Jamet

A. On its Face, the Cited Art Fails to Make a *Prima Facie* Case of Obviousness

Claims 27 and 31-37 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Patten (Current Opinion in Biotechnology, 8:724-733, December 1997) and Jamet *et al.* (Journal of Molecular Evolution, 33:226-236, 1991). According to the Patent Office, Patten *et al.* “teach at length of the benefits and broad applicability [of DNA shuffling]” to “genes, including genes that exist in subunits.” [Official Action at page 10.] The Patent Office admits that “**Patten et al. do not explicitly teach of performing DNA shuffling on the parental polynucleotides of RUBISCO (ribulose-1,5-bis-phosphate carboxylase).**” [Official Action at page 10.] Because Patten does not teach or suggest applying the disclosed method(s) to RUBISCO, Patten is a **general** disclosure.

To make up for the lack of any specificity in Patten, the Patent Office cites to Jamet *et al.* for allegedly teaching “at length of the genes encoding RUBISCO . . . and subunits thereof. [Official Action at page 10.] However, Jamet does not broadly teach about the genes encoding RUBISCO. Jamet, which is entitled “Genes Encoding the **Small Subunit of RUBISCO** Belong to Two Highly Conserved Subfamilies in **Nicotianae**,” is limited to only disclosures regarding the “small subunit” (S-subunit) of RUBISCO. In contrast, the Applicants’ specification discloses that the large subunits of RUBISCO are catalytically active and that the S-subunit is merely a “complementing” subunit that in certain instances, renders the large subunit (L-subunit) of RUBISCO catalytically active:

The Calvin cycle utilizes, e.g., the enzyme rubisco (ribulose-1,5-bisphosphate carboxylase/oxygenase). Rubisco exists in at least two forms: form I rubisco is found in proteobacteria, cyanobacteria, and plastids, e.g., as an **octo-dimer composed of eight large subunits, and eight small subunits**; form II rubisco is a dimeric form of the enzyme, e.g., as found in proteobacteria. **Form I rubisco is encoded by two genes (rbcL and rbcS,) while form II rubisco has clear similarities to the large subunit of form I rubisco, and is encoded by a single gene, also called rbcL.** The evolutionary origin of the small subunit of form I rubisco remains uncertain; it is less highly conserved than the large subunit, and may have cryptic homology to a portion of the form II protein.

[Specification at page 3, lines 6-15; emphasis added in bold.]

* * *

Although the method is believed broadly applicable to evolving biosynthetic enzymes having desired properties, the invention is described principally with reference to the metabolic enzyme activities of plants and/or photosynthetic microbes defined as ribulose-1,5-bisphosphate carboxylase/oxygenase ("Rubisco"), including both **regulatory subunit (small subunit, S;** gene designation, rbcS) and **catalytic subunit (large subunits L;** gene designation, rbcL), respectively, as appropriate for Form I (L₈S₈) and Form II (L₂) Rubisco.

[Specification at page 5, lines 11-18; emphasis added in bold.]

* * *

In an aspect, the enhanced Rubisco protein is often a **L subunit which is catalytically active** in the presence of a **complementing S subunit**. In an aspect, the enhanced Rubisco protein is a **L subunit which is catalytically active in the absence of a complementing S subunit**, such as for example and not limitation a Rubisco L subunit which is at least 90 percent sequence identical to a naturally occurring Form II L subunit.

[Specification at page 6, lines 17-22; emphasis added in bold.]

Thus, the Applicants' specification discloses that the small subunit proteins of Jamet, which are complementing rather than catalytic, do not satisfy the limitation in Applicants' independent claim 27 to "recombining a plurality of parental polynucleotide species encoding at least one protein having Rubisco carboxylation activity." The disclosure in the Applicants' specification is also corroborated by the art cited by the Patent Office. In particular, Spreitzer also discloses that only the large subunits are "catalytic." [Spreitzer at page 428 ("The fact that large subunits can perform carboxylation in the complete absence of small subunits would indicate that the requisite structure for catalysis resides solely on the large subunit.")]. For these reasons, the combination of Patten over Jamet would not render obviousness the Applicant's claimed method as a whole. *See Jones v. Hardy*, 220 USPQ 1021, 1025 (Fed. Cir. 1984) ("The test under § 103 is not whether an improvement or use set forth in a patent would have been obvious or nonobvious. The test is whether the **claimed invention**,

considered as a whole, would have been obvious or non-obvious.”); emphasis added in bold. For these reasons, the rejection of claims 27 and 31-37 under 35 U.S.C. § 103(a) for allegedly being unpatentable over Patten and Jamet is legally erroneous.

B. There is No Suggestion or Compelling Motivation in the Art to Perform the Method of Applicants’ Claims

Separately, as reflected in Jamet’s title, Jamet is directed to disclosing that in *Nicotania*, the “small subunits of RUBISCO belong to Two Highly Conserved Subfamilies.” There is no suggestion or motivation to modify an entire RUBISCO enzyme, which is either Form I (L₈S₈) and Form II (L₂) and requires the large (L) catalytic subunits, because the large catalytic subunits are neither disclosed nor discussed. As its sole source of motivation, the Patent Office relies upon a statement by the Applicants’ taken out of context. Specifically, the Patent Offices cites to the statement at page 3 of the Applicants’ specification regarding the “fundamental importance” of RUBISCO of photosynthesis:

All photosynthetic organisms catalyze the fixation of atmospheric CO₂ by the bifunctional enzyme ribulose 1,5-bisphosphate carboxylase/oxygenase (“Rubisco”; EC 4.1.1.39). Significant variations in kinetic properties of this enzyme are found among various phylogenetic groups. Because of the abundance and **fundamental importance** of Rubisco, the enzyme has been extensively studied. Well over 1,000 different Rubisco homologues are available in the public literature (e.g., over 1,000 different Rubisco homologues are listen in GenBank alone), and the crystal structure of Rubisco has been solved for several variants of the protein.

[Specification at page 3, lines 21-28; emphasis added in bold.]

However, in the Patent Office’s version of the above quotation, the first two sentences which provided the context for the phrase “fundamental importance” were deleted. These two sentences reflect that the phrase “fundamental importance” related back to “photosynthe[sis].” The mere fact that something is fundamentally important in photosynthesis [to plants] does not automatically mean that one would be motivated from a patent perspective to tinker with the enzyme to further improve upon it. For example, the neurotoxin in the venom of the Southern Pacific Rattlesnake is of **fundamental importance** for its survival. The neurotoxin stops the

rattlesnake's prey from moving too far away after being bitten. The "fundamental importance" of this neurotoxin component [to the snake] does not mean that one would be motivated to modify the neurotoxin to improve upon its neurotoxicity. Moreover, the Applicants' own statement of the "fundamental importance" of the enzyme in photosynthesis does not take the place of the prior art. *See In re Dow Chemical*, 5USPQ2d 1529, 1531 (Fed. Cir. 1988) ("Further, a patent applicant's statement of the purpose of the work is not prior art."). In the present cited art, there is no "suggestion" or "compelling motivation" based upon sound scientific principles for one skilled in the art to employ the method that the Applicant has done. *See Ex parte Kranz*, 19 USPQ2d 1216, 1218 (Fed. Cir. 1991) ("Before obviousness may be established, the examiner must show that there is either a suggestion in the art to produce that claimed invention or a compelling motivation based upon sound scientific principles."). For all these reasons, there is no suggestion or compelling motivation **found in the prior art** to combine the cited references to make the Applicants' claimed method. Moreover, as noted in Section A above, even if the references are combined, they fail to make a *prime facie* case of obviousness of the invention as a whole.

To the extent that the Patent Office interprets the Applicants' statement of "fundamental importance" as indicating a "long felt need" in the field, it is evidence of non-obviousness rather than obviousness. *See In re Dow Chemical*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988) ("The PTO's reliance on Dow's 'admission' of longfelt need as *prima facie* evidence of obviousness is contrary to logic and the law. Recognition of need, and difficulties encountered are classical indicia of nonobviousness."). For all these reasons, the evidence and art of record fails to make a *prima facie* case of obviousness against claims 27 and 31-37 of the claimed invention.

C. The Prior Art as a Whole Fails to Provide the Requisite "Reasonable Expectation of Success"

"The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art." *In re Dow Chemical*, 5USPQ2d 1529, 1531 (Fed. Cir. 1988). "Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure."

Amgen v. Chugai, 18 USPQ2d 1016, 1207 (Fed. Cir. 1991). “While absolute certainty is not necessary to establish a reasonable expectation of success, [citation omitted], there can be little better evidence negating an expectation of success than actual reports of failure.” *Boehringer Ingelheim v. Schering-Plough Corp.*, 320 F.3d 1339, 1354 (Fed. Cir. 2003).

In the present case, the Patent Office cites to a **long felt need** and a **general** teaching in the art [Patten] to conclude that there would be a reasonable expectation of success:

In view of the admitted well documented interest in RUBISCO [*i.e.*, **longfelt need**], the “fundamental importance” that it possesses, one of ordinary skill in the art would have been motivated to have been amply motivated to have subjected parental polynucleotide species that encode RUBISCO to DNA shuffling such that optimized RUBISCO could be obtained and isolated. In view of the explicit guidance, and broad applicability of DNA shuffling to **proteins in general**, the ordinary artisan would have had a most reasonable expectation of success.

[Official Action at page 10; emphasis added in bold.]

Thus, the Patent Office has acknowledged above that Patten’s disclosure applies to “**proteins in general**” rather than having any specificity to RUBISCO.

Assuming for the sake of argument that a *prima facie* case of obviousness had been made, it is rebutted by the Applicants’ **specific evidence** on RUBISCO, which must be considered anew with all of the evidence of record.

When prima facie obviousness is established and evidence is submitted in rebuttal, the decision-maker must start over. * *

*** An earlier decision should not, as it was here, be considered as set in concrete, and applicant's rebuttal evidence then be evaluated only on its knockdown ability. Analytical fixation on an earlier decision can tend to provide that decision with an undeservedly broadened umbrella effect. Prima facie obviousness is a legal conclusion, not a fact. Facts established by rebuttal evidence must be evaluated along with the facts on which the earlier conclusion was reached, not against the conclusion itself. * * ***

[*In re Piasecki*, 223 USPQ 785, 788 (Fed. Cir. 1984) citing *In re Rinehardt*, 189 USPQ 143, 147 (CCPA 1976); emphasis added in bold.]

Thus, any evidence submitted by the Applicants must cause the Patent Office to start over, eliminate any legal conclusion of obviousness, and consider whether the factual evidence as a whole would still make a *prima facie* case of obviousness. In the present case, the Applicants are submitting in rebuttal, several references which are specific for RUBISCO.

In determining the weight that is to be applied to the references cited by the Applicants or the Patent Office, the courts have held (and logic dictates) that “**specific**” references are to be given more weight than the “**general**” teachings in the art which are inherently less specific. See *In re Lunsford*, 148 USPQ 721, 724 (CCPA 1966) (reversing the Board's conclusion of obviousness where the board relied on the “general” teachings of the prior art while ignoring the “specific” teachings, stating: “Thus, the Examiner erred in *ignoring* the specific teachings of the primary references **without references containing specific teachings demonstrating that the specific teachings in Biel I and III could be ignored.**”) [Emphasis added in bold].

Likewise, in another case, *In re Fournet*, 148 USPQ 740, 742 (CCPA 1966), the CCPA again held that “specific” teachings are entitled to “**greater weight**” than “general” teachings, stating:

We regard the use of the prior art teachings under 35 U.S.C. § 103 as a two-way street available to both parties. We are required to evaluate the references *as a whole* regardless of the party offering the references. In *Lunsford*, we refuse to ignore **specific teachings which we believed would be given greater weight than general teachings by one of ordinary skill in the art.**

We evaluated the references against the invention as a whole, as required by 35 U.S.C. § 103, and **gave effect to the uncontroverted specific teachings which were contrary to the position of the Patent Office.**

[Emphasis added in bold.]

Similarly, in *In re Tomlinson*, the CCPA held that one skilled in the art would consider the “specific” teachings in the art to be the most pertinent and would accord them the most weight:

It seems to be that **the specific teachings** in Italian, Tholstrup, etc. relied upon by the Patent Office **are the 'teachings which a person of ordinary skill in the art would consider the most pertinent and accord the most weight'** as they are 'closely concerned with the claimed invention.

[*In re Tomlinson*, 150 USPQ 623, 630 (CCPA 1966) *citing In re Lunsford*, 148 USPQ 721, 724 n. 1 (CCPA 1966); emphasis added in bold.]

Thus, as a matter of law, the “specific” teachings of the prior art (*i.e.*, those teachings that are most closely concerned with the claimed invention) must be considered the most pertinent and accorded more weight than “non-specific” or “general” teachings.

As discussed above, the Patent Office relies upon the “general” reference, Patten *et al.*, which the Patent Office admits “**do not explicitly teach of performing DNA shuffling on the parental polynucleotides of RUBISCO (ribulose-1,5-bis-phosphate carboxylase)**” but rather discloses “broad applicability of DNA shuffling to **proteins in general.**” [Official Action at page 10.] In contrast to the general teaching relied upon by the Patent Office, the Applicants cite to and rely upon **specific teachings** on RUBISCO and other **specific factual evidence** by one skilled in the art (the Zhu Declaration) that disclose the prior failed attempts by others at improving RUBISCO and whether there would be a “reasonable expectation of success” in obtaining a RUBISCO gene with enhanced carboxylation activity relative to the parental gene(s).

As their first specific reference, the Applicants cite to Mann, “Genetic Engineers Aim to Soup Up Crop Photosynthesis,” *Science* 283:314-316 (January 15, 1999), which is already of record and cited in the Applicants’ IDS dated 02/27/04. In particular, Mann, which is a report on the history and future, discloses a “longfelt need” since the 1970s, “failure by others” and lack of a “reasonable expectation of success”:

RuBisCO’s ineffectiveness has been a spur to scientists since it became fully apparent in the 1970s. Indeed, the quest for a better RuBisCO is a “Holy Grail in plant biology” says George Lorimer, a biochemist at the University of Maryland, College Park, who worked with the Swedish team that mapped the enzyme’s structure in 1984. “Everyone always goes in with the hope of changing the face of agriculture.” Despite more than 20 years of effort, the hopes have not yet paid off.

[Mann at pages 314-315 (bridging paragraph); emphasis added in bold.]

* * *

“**We spent years** creating high resolution structures of spinach [a model plant in RuBisCO research] and cyanobacteria,” says Lorimar. But despite the finely detailed results, “**the sobering reality was that you can lay down [structural maps of] these two enzymes on top of each other and you are very hard pressed to see the differences.**” Even if the differences could be identified, Lorimar believes, they would be so numerous and subtle “that **you could not rationally reason your way to what it was that you need to improve the enzyme.**”

The **failure** of the structures to provide a path for modifying RuBisCO **dismayed many researchers**

[Mann at page 315, col. 3; emphasis added in bold.]

Thus, Mann, which is a **specific** evidence on the efforts of others to produce an improved RUBISCO, discloses a “longfelt need” since the 1970s, “failure by others” and lack of a “reasonable expectation of success” - all of which are indicia of non-obviousness.

As their second specific reference, the Applicants cite to Gewolb, “Plant Scientists See Big Potential in Tiny Plastids,” *Science* 295:258-259 (2002) which was attached to the Zhu declaration and which is cited in an IDS cofiled herewith. Gewolb was also attached to the Applicants’ Response to the Official Action of 12/28/01. Gewolb discloses that as late as 2002, which is after the Applicants’ claimed priority date, that an improved RUBISCO has yet to be made and that only a **less efficient** form of RUBISCO from red algae has been transferred to a plant:

Until the invention of plastid transformation, scientists could not tinker with RuBisCO, the key carbon fixing enzyme of photosynthesis, because half of its subunits are encoded in the chloroplast genome. **Dozens of research groups have tried to alter the molecule to improve the efficiency of photosynthesis, but none so far have succeeded** (*Science*, 15 January 1999, p. 314).

Now, however, plant physiologists . . . have taken a key step toward this goal, creating the first viable plants with an altered RuBisCO. They report . . . that photosynthetic **efficiency drops** predictably when the RuBisCO of tobacco is replaced by the less efficient RuBisCO from the red algae *Rhodospirillum rubrum*.

Even though **the plants are less efficient, not more**, the advance is exciting

[Gewolb at page 259; emphasis added in bold.]

Thus, even after the Applicants' priority filing date, the **specific** evidence on RUBISCO, such as Gewolb, discloses the continued **failure of others** to make or use a RUBISCO with enhanced carboxylation activity.

Finally, as their third piece of **specific** factual evidence, the Applicants cite to the Declaration of Genhai Zhu under 37 C.F.R. § 1.32, dated 11/13/02 ("the Zhu Declaration). In his declaration, Dr. Zhu declared that between 1992 and the date of his declaration (10/28/02), that he had performed Ph.D. level research on RUBISCO. [Zhu Declaration at ¶¶ 1-5.] Thus, Dr. Zhu is a person of ordinary skill in the RUBISCO art. Dr. Zhu declares that he had reviewed the Mann and Gewolb references cited above. [Zhu Declaration at ¶¶ 9-11.] As a person skilled in the RUBISCO art, Dr. Zhu declares that the view expressed in Mann, regarding the **lack of likelihood of success** "is entirely consistent with the view of those working in the field at the time":

10. Significantly, the Mann article does not suggest or even mention using an approach that would involve screening for an improved RUBISCO variant. This implies that the author viewed the likelihood of this approach succeeding to be even less probable than the approaches he does discuss, all of which he concedes are long shots in terms of likelihood of success. **This view is entirely consistent with the consensus opinion of those working in the field at the time, i.e., that an attempt to obtain an enhanced Rubisco by the screening of a library of variants would not be likely to succeed, and thus it would be worth trying alternate approaches that are technically challenging and not likely to succeed.**

[Zhu Declaration at ¶ 10; emphasis added in bold.]

Thus, Dr. Zhu declares that the view in the RUBISCO art as of Mann's publication date (1999) was that given the history of failures in the art, the preparing and screening of libraries of RUBISCO variants would not succeed in producing a RUBISCO with enhanced catalytic activity. Because Dr. Zhu is a person skilled in the RUBISCO art, his declared statements are

factual evidence not opinion. Hence, they cannot be dismissed by the Patent Office as opinion. Rather, they require **specific** factual evidence to be rebutted.

When all of the evidence of record is considered, including the **specific** factual evidence cited above by the Applicants, it rebuts any **general** evidence [Patten] relied upon by the Patent Office. Moreover, the above factual evidence establishes the “longfelt need” in the art, the failure of others, and the lack of a reasonable expectation of success. These are all indicia of non-obviousness and would rebut any *prima facie* case of obviousness. *See In re Dow Chemical*, 5 USPQ2d at 1531 (“Recognition of need, and difficulties encountered by those skilled in the field are classical indicia of unobviousness.”). For all these reason, any rejection of claims 27 and 31-37 under 35 U.S.C. § 103(a) for obviousness over Patten and Jamet has been rebutted. The withdrawal of this basis for rejection is respectfully requested.

D. The Patent Office Errs in Requiring that the Applicants Provide “Convincing Evidence to the Contrary”

The Applicants’ burden of proof in prosecution before the Patent Office is simply that the Applicants must prove facts by a “**preponderance of evidence.**” *See In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992) (“After evidence or argument is submitted by the applicant in response, patentability is determined on a totality of the record, by a **preponderance of evidence** with due consideration to persuasiveness of argument.” (emphasis added in bold)). As a matter of law, “[a] preponderance of the evidence standard . . . simply requires the trier of fact ‘to believe that the **existence** of a fact is **more probable** than its **nonexistence** before he may find in favor of the party who has the burden to persuade the judge of the fact’s existence.’” *Price v. Symsek*, 26 USPQ2d 1031, 1035 (Fed. Cir. 1993) (emphasis added in bold). Thus, the Applicants need demonstrate only that it is more likely than not (*i.e.*, to a 51% degree of certainty) that the claimed method produces a RUBISCO with greater activity than that encoded by the parental polynucleotide.

In contrast, the Courts have recognized that “clear and convincing evidence” standard, such as imposed upon the Applicants by the Patent Office, places a higher burden of persuasion on the Applicants than required by law:

A requirement of proof by **clear and convincing evidence** imposes a **heavier burden** upon a litigant **than** that imposed by requiring

proof by preponderant evidence but a somewhat lighter burden than that imposed by requiring proof beyond a reasonable doubt.

[*Price*, 26 USPQ2d at 1034; emphasis added in bold.]

In contrast to the correct **preponderance** standard, which only requires proof sufficient for a trier of fact to believe that a fact is “**more likely than not**” (to a 51% likelihood), the “**clear and convincing**” standard requires proof sufficient for a trier of fact to believe that a fact is “**highly probable**”:

“**Clear and convincing**” evidence has been described as evidence which produces in the mind of the trier of fact an abiding **conviction that the truth of a factual contention** is “**highly probable**”.
[Citations omitted.]

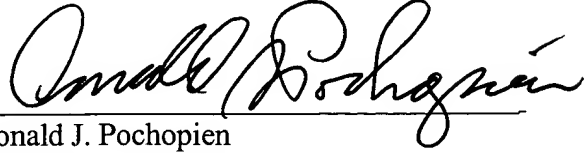
[*Price*, 26 USPQ2d at 1034; emphasis added in bold.]

Further, in *Price*, the Federal Circuit held that the Board erred when it required *Price* to prove a fact under the higher legal standard. *Price*, 26 USPQ2d at 1036. Moreover, the Court found that the imposition of the “clear and convincing standard” was **not** “harmless error.” *Price*, 26 USPQ2d at 1036 (“the erroneous burden of proof utilized by the Board worked against *Price*’s interest, *i.e.*, it was more difficult to overcome than the proper burden of proof. **Such a situation cannot ordinarily be classified as ‘harmless.’**”). Likewise, in the present situation, the Patent Office’s imposition of the “clear and convincing evidence” standard upon the Applicants cannot be classified as “harmless error.” When the proper standard is applied and all of the evidence of record considered, it is more likely than not that the claims 27 and 31-37 would **not** have been obvious over the prior art as a whole. The allowance of claims 27 and 31-37 is respectfully requested.

Respectfully submitted,

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By:

A handwritten signature in cursive script, appearing to read "Donald J. Pochopien", written over a horizontal line.

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